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Efficacy of the Intraoperative Use of Indocyanine-Green Fluorescence Angiography in Laparoscopic Rectal Resections

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Abstract

Background: In traditional laparoscopic colorectal cancer surgery, the surgeon's method assess intestinal stumps blood supply is subject to certain subjectivity and blindness. Indocyanine green (ICG) real-time blood perfusion fluorescence angiography in laparoscopic radical resection of rectal cancer has great potential clinical value and can visually judge intestinal tract blood supply to improve the surgery safety, reduce postoperative complications, and ensure the recovery of patients after surgery. **Objective:** To explore the efficacy of the intraoperative use of indocyanine-green fluorescence angiography in laparoscopic rectal resections in patients with rectal cancer. **Methods:** In the present study, 109 rectal cancer patients were included and assigned to different surgical groups [ICG and control groups] for analysis. Statistical analysis was carried out for various common postoperative complications in the two groups. Finally, the patients in the ICG fluorescence imaging group had a timely adjustment of the proximal resection of the intestinal tube before the proximal bowel of the lesion was cut off when the intestinal blood supply was insufficiently assessed by fluorescence imaging. Two subgroups, the adjustment and the non-adjustment groups, were analyzed. **Results:** Compared with the control group, the postoperative anal ventilation time in the ICG group was shorter than that in the control group ($P < 0.05$). In addition, the postoperative complications were lower than those in the control group, and the differences were statistically significant ($P < 0.05$). However, the distance between the tumor from the anal verge in the adjustment group was smaller than that in the non-adjustment group, and the difference was statistically significant ($P < 0.01$). **Conclusion:** Compared with conventional laparoscopic

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radical resection of rectal cancer, ICG real-time indocyanine green fluorescence angiography was safe and feasible. This technique is a promising intraoperative tool for the assessment of bowel perfusion especially suitable for patients with lower rectal cancer.

Keywords

Laparoscopic Rectal Resection, Indocyanine, Rectal Cancer

1. Introduction

Rectal cancer is one of the most common malignant tumors of the digestive tract. In recent years, the incidence of rectal cancer has increased, and it has the characteristics of a low location and young age. It has become one of the major malignant tumors that seriously threaten human health. Surgical resection is still the main treatment method for rectal cancer. With the continuous progress of minimally invasive surgery and the rapid development of surgical techniques and equipment, the radical cure of rectal cancer and the survival rate of patients are improving. However, anastomotic leakage after rectal surgery is still one of the most serious complications. The incidence of anastomotic leakage after rectal cancer surgery ranges from 1% to 20%. Postoperative anastomotic leakage increases the reoperation rate, hospital stay, and postoperative mortality risk and adversely affects patient outcomes [1] [2] [3] [4] [5]. There are many reasons for anastomotic leakage closely related to factors such as low anastomosis, male sex, preoperative radiotherapy and chemotherapy, anastomotic technique, anastomotic tension, anastomotic tissue blood supply, and systemic nutritional status [6] [7]. Among them, the blood supply of the anastomotic stoma is one of the indicators observed and optimized during the operation, but traditional naked-eye observation has a certain degree of subjectivity, and the accuracy needs to be discussed [8]. Real-time blood perfusion fluorescence imaging combined with indocyanine green (ICG) during radical resection for rectal cancer can objectively determine intestinal canal blood perfusion around the anastomosis, bringing great benefits to rectal cancer surgical treatment [9] [10]. We collected clinical data of patients who underwent ICG real-time vascular fluorescence imaging during laparoscopic radical rectal cancer surgery in our department from October 2020 to March 2022. We analyzed, compared, and reported the clinical application of ICG real-time blood flow perfusion fluorescence imaging in laparoscopic radical rectal cancer surgery.

2. Materials and Methods

2.1. General Clinical Information

The data of 109 patients who underwent laparoscopic radical resection of rectal cancer in this operation group from October 2020 to March 2022 in the Ga-

strointestinal Surgery of Chongqing University Affiliated Cancer Hospital were collected. The patients were divided into groups according to whether ICG real-time blood flow perfusion fluorescence imaging was performed during the operation. For the ICG fluorescence imaging group and the control group, the ICG fluorescence imaging group underwent ICG real-time blood flow perfusion fluorescence imaging in laparoscopic radical rectal cancer surgery. In contrast, the control group only underwent laparoscopic radical rectal cancer surgery. There were 52 patients in the ICG fluorescence imaging group, aged between 52 and 72 years old, and 57 patients in the control group, aged between 50 and 73 years old. All patients underwent routine colonoscopy pathological biopsy, enhanced chest-abdominal-pelvic CT., and serum tumor marker monitoring. The patients were diagnosed with rectal cancer before surgery. All patients completed the operation under laparoscopy, and no patient was converted to laparotomy. The following patients were excluded: 1) Distant metastases to the liver, lungs, and other distant organs; 2) Intestinal obstruction not relieved before surgery; 3) Heart, brain, lung, and other organs insufficient and could not tolerate laparoscopic surgery; 4) Combined organ resection that required and emergency surgery; and 5) patients allergic to indocyanine green. Both groups of patients signed informed consent for laparoscopic surgery.

2.2. Surgical Methods

The same fixed operation group performed all operations in gastrointestinal surgery. The chief surgeon was experienced in laparoscopic surgery. The patient received oral sodium phosphate oral solution for bowel preparation the night before surgery, and prophylactic intravenous antibiotics were administered 30 minutes before surgery. General anesthesia with tracheal intubation and routine catheterization were routinely used in all operations. Fluorescence laparoscopy uses the Stryker high-definition laparoscopic surgical fluorescence system. Both groups of patients underwent standardized laparoscopic radical rectal resection procedures, strictly following the principles of total mesentery resection and standardized lymph node dissection. The excised specimens were removed from the lower abdominal auxiliary small incision. In the ICG group, 25 mg of indocyanine green was diluted in 10 ml of normal saline, and a 3 ml dose was rapidly injected into the peripheral blood vessels. Real-time blood perfusion was evaluated and recorded by fluorescence imaging before dissection, placement of the stapler, and after anastomosis (**Figure 1**). In the ICG group, when the intestinal blood supply was insufficiently assessed by fluorescence imaging before the intestinal canal was severed, the operator adjusted the intestinal canal to the site with good blood supply according to the intestinal fluorescence imaging. Then, the operator separated the intestinal canal. After the digestive tract reconstruction was completed, the anastomotic intestinal blood was re-evaluated for perfusion confirmation. The control group used the conventional high-definition laparoscopic system, adopted the same surgical separation method and anastomosis

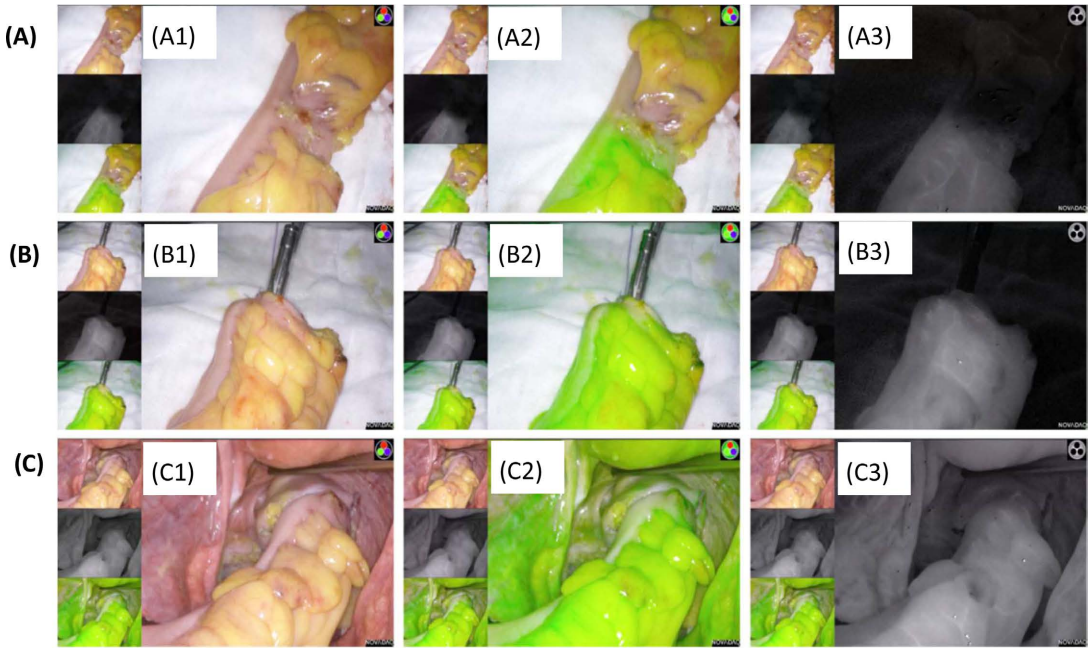

Figure 1. Real-time blood perfusion of the rectum was evaluated and recorded by fluorescence imaging before dissection, placement of the stapler, and after anastomosis. (A) View before dissection with standard light (A1), green fluorescence (A2), and white light (A3); (B) View before placement of the stapler with standard light (B1), green fluorescence (B2), and white light (B3); (C) View after anastomosis with standard light (C1), green fluorescence (C2), and white light (C3).

method, and completed the anastomosis through the surgeon's naked eye assessment of the intestinal blood supply.

2.3. Data Collection

The sex, age, anesthesia classification (ASA), body mass index (BMI), preoperative stage, smoking history, diabetes history, neoadjuvant chemoradiotherapy history, abdominal surgery history, and the distance from the tumor to the anus were compared and analyzed between the two groups. The operation time (from skin incision to the end of skin suture), intraoperative blood loss (anesthesia record sheet), postoperative anal ventilation time, postoperative hospital stay, C-reactive protein value on the first postoperative day, number of lymph nodes dissected, postoperative pathological and TN staging were compared between the two groups of patients. For statistical analysis, the common perioperative complications, such as postoperative intestinal obstruction, abdominal hemorrhage, incision infection, abdominal infection, anastomotic leakage, and anastomotic bleeding were recorded. In the ICG fluorescence imaging group, before the proximal bowel of the lesion was severed, the scope of the proximal bowel resection was adjusted in time when the intestinal blood supply was insufficiently assessed by fluorescence imaging. Whether the proximal margin adjustment was performed during the operation, the patients were divided into adjusted and unadjusted subgroups, for analysis. Sex, age, anesthesia classification (ASA), body mass index (BMI), preoperative stage, smoking history, diabetes history,

neoadjuvant chemoradiotherapy history, abdominal surgery history, and the distance between the tumor and the anus were compared between the two subgroups of patients.

2.4. Statistical Analysis

SPSS 18.0 software was used for statistical analysis of the clinical data of all patients. The measurements are expressed as the mean ± standard deviation ($x \pm s$), and a T test was used for statistical analysis. The enumeration data are expressed as percentages, and the χ^2 test was used for statistical analysis. $P < 0.05$ indicated a statistically significant difference.

3. Results

3.1. Comparative Analysis of General Clinical Data

There was no significant difference in terms of sex, age, anesthesia classification (ASA), body mass index (BMI), preoperative stage, smoking history, diabetes history, neoadjuvant chemoradiotherapy history, abdominal surgery history, or tumor distance from the anus between the ICG group and the control group in the general data of the two groups of patients ($p > 0.05$). The two groups were comparable (Table 1).

Comparison of intraoperative and postoperative conditions

Radical resection of rectal cancer was completed under laparoscopy in all cases, and there was no case of conversion to laparotomy. Although there were no significant differences in intraoperative blood loss, operation time, postoperative hospital stay, C-reactive protein value on the first postoperative day, number of lymph nodes dissected, postoperative pathological or TN staging between the two groups ($P > 0.05$), the postoperative exhaust time in the ICG fluorescence imaging group was shorter than that in the control group, and the difference was

Table 1. Characteristics of patients.

Variables	ICG group (n = 52)	Control group (n = 57)	P value
Male:Female	33:19	26:31	0.062
Age (years)	61.85 ± 9.82	62.21 ± 11.45	0.861
ASA score (≥3)	35 (67.31%)	34 (59.65%)	0.407
BMI (≥25 kg/m^2)	15 (28.85%)	20 (35.09%)	0.486
Clinical T status 3 - 4	41 (78.85%)	44 (77.19%)	0.835
Smoking history	17 (32.69%)	13 (22.81%)	0.248
Diabetes	6 (11.54%)	4 (7.02%)	0.514
Neoadjuvant therapy	5 (9.62%)	5 (8.77%)	0.879
Previous abdominal surgery	10 (19.23%)	11 (19.30%)	0.993
Tumor distance from anal verge (cm)	7.91 ± 3.30	8.12 ± 3.29	0.740

Table 2. Tumor and operative characteristics.

Variables	ICG group (n = 52)	Control group (n = 57)	P value
Intraoperative blood loss(ml)	48.27 ± 17.35	54.21 ± 20.78	0.110
Operation time (min)	206.67 ± 43.66	217.09 ± 59.81	0.305
Postoperative anal gas evacuation time (d)	2.69 ± 0.81	3.14 ± 0.77	0.004
Postoperative hospital stay (d)	9.98 ± 4.00	10.06 ± 5.72	0.933
CRP level on the first day after surgery (mg/L)	31.47 ± 28.29	29.22 ± 23.72	0.653
Number of dissected lymph nodes (n)	13.88 ± 6.67	12.23 ± 4.44	0.128
Pathological T status 3 - 4	37 (71.15%)	41 (71.93%)	0.929

statistically significant ($P < 0.05$) (Table 2).

3.2. Comparison of Postoperative Complications

There were no postoperative deaths in either group of patients, and no patients with indocyanine green allergy were found in the ICG fluorescence imaging group. No anastomotic leakage occurred in the ICG fluorescence imaging group. However, 3 patients in the control group developed anastomotic leakage, which was cured and discharged after conservative treatment. There was no anastomotic bleeding in the ICG fluorescence imaging group and 1 case in the control group. There was no patient with intestinal obstruction in the ICG fluorescence imaging group. Two patients in the control group developed intestinal obstruction. They were cured and discharged after conservative treatment, considering postoperative inflammatory intestinal obstruction. There was 1 case of abdominal infection in the ICG fluorescence imaging group and 3 cases of abdominal infection in the control group. There was 1 case of incision infection in each of the two groups; 1 case in the ICG fluorescence imaging group developed urinary retention, and 2 cases in the control group experienced urinary retention. The total incidence of postoperative complications in the ICG fluorescence imaging group was 5.78%, which was lower than that in the control group, which was 21.05% ($p < 0.05$) (Table 3).

3.3. Subgroup Analysis in the ICG Fluoroscopy Group

In the ICG fluorescence imaging group, before the proximal bowel of the lesion was severed, the scope of the proximal bowel resection was adjusted in time when the intestinal blood supply was insufficiently assessed by fluorescence imaging. Based on this, fifty-two patients were divided into two subgroups, fluorescence-adjusted and nonadjusted, according to whether near margin adjustment was performed during the operation and analyzed and compared into two subgroups. The results showed no differences in sex, age, anesthesia classification (ASA), body mass index (BMI), clinicopathological stage, smoking history, diabetes history, neoadjuvant chemoradiotherapy history, or abdominal surgery

Table 3. Postoperative complications.

Variables	ICG group (n = 52)	Control group (n = 57)	P value
Postoperative complications, n (%)	3 (5.78%)	12 (21.05%)	0.021
Anastomotic leak	0	3	
Anastomotic bleeding	0	1	
Bowel obstruction	0	2	
Abdominal infection	1	3	
Surgical incision infection	1	1	
Urinary retention	1	2	
ICG allergy	0	0	
Reoperation, n	0	0	
Mortality, n	0	0	

Table 4. Factors associated with the adjustment of transection sites.

Variables	adjustment group (n = 23)	non-adjustment group (n = 29)	P value
Male:Female	13:10	20:9	0.355
Age (years)	62.91 ± 10.48	61.00 ± 9.36	0.317
ASA score (≥3)	13 (52.17%)	22 (79.31%)	0.140
BMI (≥25 kg/m^2)	6 (26.09%)	9 (31.03%)	0.696
Pathological T status 3 - 4	14 (60.88%)	23 (79.31%)	0.145
Smoking history	6 (26.09%)	11 (37.93%)	0.366
Diabetes	1 (4.35%)	5 (17.24%)	0.210
Neoadjuvant therapy	2 (8.70%)	3 (10.34%)	0.841
Previous abdominal surgery	3 (13.04%)	7 (24.14%)	0.482
Tumor distance from anal verge (cm)	5.39 ± 1.97	9.91 ± 2.72	P < 0.001

history between the two subgroups of patients. However, the distance from the tumor to the anus in the fluorescence-adjusted group was smaller than that in the nonadjusted group, and the difference was statistically significant (P < 0.01) (Table 4).

4. Discussion

Anastomotic leakage has been one of the most important postoperative complications in colorectal surgery for a long time. Insufficient blood supply to the anastomotic stoma is the most critical factor for anastomotic leakage in colorectal cancer surgery. Minimizing the risk of anastomotic leakage is an essential goal pursued by intestinal surgeons. In traditional laparoscopic surgery, the

surgeon's method of assessing the intestinal stump blood supply is mainly performed with the naked eye. For example, during the operation, the surgeon observes whether the color of the bowel is ruddy, whether there is active bleeding at the incision margin, whether the mesenteric vascular arch is complete, and whether there is a fluctuation of the mesenteric blood vessels. However, intraoperative observation methods have certain subjectivity and blindness. In addition, the judgment of the blood supply of anastomosis is time-consuming and lacks accuracy [8].

Indocyanine green (ICG), a medical water-soluble fluorescent dye that isnontoxic to the human body and has good affinity, has near-infrared absorption and fluorescence emission characteristics. It can emit visible fluorescence that can be monitored. At present, ICG has been widely used in the visualization of the cardiovascular system, retina and choroid, ophthalmology, and cerebral angiography [11] [12]. In addition to organ function testing and vascular imaging, ICG has recently been increasingly used to assess blood perfusion and tumor imaging. The clinical application of ICG fluorescence imaging technology in colorectal cancer surgery is increasing, bringing great benefits to colorectal surgery [13] [14]. As a simple and effective method for evaluating tissue perfusion in laparoscopic surgery, ICG fluorescence imaging technology can display the blood perfusion of the tissue in real-time during the operation. Furthermore, it has the advantage of indocyanine green in white light mode without coloration. The drug is cheap, safe, nontoxic, and guaranteed operations such as lesion resection and lymph node dissection in routine laparoscopic colorectal cancer surgery [15] [16]. A multicenter cohort study showed that the application of ICG fluorescence imaging technology in colorectal cancer is safe and reliable. This technology significantly reduces the incidence of laparoscopic colorectal cancer anastomotic leakage and the rate of unplanned surgery [17].

A total of 109 patients who underwent laparoscopic radical resection of rectal cancer were included in this study. They were divided into an ICG fluorescence imaging group and a control group according to whether ICG real-time blood flow perfusion fluorescence imaging was performed during the operation. The two groups of patients were comparable in terms of general data, such as sex, age, anesthesia grade (ASA), body mass index, preoperative stage (BMI), smoking history, history of diabetes, history of neoadjuvant radiotherapy and chemotherapy, history of abdominal surgery, and distance from the tumor to the anus. All the patients in the two groups completed radical resection of rectal cancer under laparoscopy. There were no conversions to laparotomy and no deaths. Our study found that although there were no differences in intraoperative blood loss, operation time, postoperative hospital stay, C-reactive protein value on the first postoperative day, number of lymph node dissections, postoperative pathological and TN staging between the two groups, the postoperative anal exhaust time in the ICG fluorescence imaging group was less than that in the control group. This indicates that the application of ICG fluorescence imaging in rectal

cancer is safe and reliable and has the potential advantage of quick recovery of bowel function. The study analyzed the postoperative complications of the two groups of patients and found no patients with secondary surgery in either group. The main complications were intestinal obstruction, incision infection, abdominal infection, anastomotic leakage, anastomotic bleeding, etc. There were 3 cases of anastomotic leakage in the control group; compared with that, there was no anastomotic leakage in the ICG fluorescence imaging group. However, this study failed to show a significant difference. Considering that it is mainly related to the number of cases and that blood perfusion is only one of the main factors leading to anastomotic leakage, other factors, such as intestinal tension, cannot be ignored. Similar conclusions were drawn by Kawada *et al.*, who noted that those who underwent anterior rectal resection had a 12% incidence of clinical anastomotic leakage, similar to their historical cohort [18]. Kin *et al.* showed no difference in anastomotic leak rates in their case-matched comparisons [19]. However, our study found that the total incidence of postoperative complications in the ICG fluorescence imaging group was significantly lower than in the control group. The analysis may be related to the reduction of complications such as inflammatory bowel obstruction and abdominal infection caused by potential anastomotic leakage by ICG fluorescence imaging.

In addition, in patients with ICG fluorescence imaging, we adjusted the proximal resection of the bowel on time when the intraoperative assessment found that the intestinal blood supply was insufficient. Accordingly, patients with ICG fluorescence imaging were divided into two subgroups, fluorescence-adjusted and nonadjusted, according to whether near-margin adjustment was performed during surgery, and the two groups were analyzed. The results showed no significant differences in sex, age, anesthesia grade (ASA), body mass index (BMI), clinicopathological stage, smoking history, diabetes history, neoadjuvant chemoradiotherapy history, or abdominal surgery history between the two subgroups. However, the distance from the tumor to the anus in the fluorescence-adjusted group was significantly smaller than that in the nonadjusted group, and the difference was statistically significant. This also illustrates the unreliability of routine macroscopic perfusion assessment in mid-low rectal cancer surgery. The distance between the tumor and the anal verge is an essential factor. The closer the tumor is to the anus, the longer the length of the proximal bowel remains, the easier it is to reduce the bowel's blood supply, and the more likely anastomotic leakage occurs. These patients may need more ICG fluorescence imaging to determine the blood supply of the anastomosis. Previous studies also showed that the incidence of anastomotic leakage was significantly reduced by half in the fluorescence group (19% vs. 9%); in particular, the number of grades A fistulas decreased, while the total number of clinically manifested grade B and C fistulas did not differ between groups. ICG fluorescence application may further reduce the occurrence of subclinical fistulas, which may lead to increased postoperative complications, such as abdominal infection, incomplete intestinal obstruction,

and the slow recovery of postoperative intestinal function [20]. This also explains the low postoperative complications and short anal ventilation time in the ICG fluorescence imaging group in our study. The above research shows that patients with tumors located closer to the anus are more likely to benefit more from ICG fluorescence.

However, most current studies comparing ICG fluorescein angiography with routine assessment are based on the characterization of ICG fluorescence in the colon wall or mucosa [21] [22]. However, qualitative evaluation may have a certain bias in accurately distinguishing the changes in colorectal microcirculation. There are very little data using quantitative analysis in the literature. Studies have found that quantitative blood flow analysis may better measure changes in colonic blood flow and microcirculation [23]. Animal experiments and clinical studies using fluorescence imaging have shown that decreased microcirculation leads to intestinal necrosis. However, the results of quantitative analysis are affected by the patient's perfusion state and by the characteristics of the fluorescence camera system and the video recording conditions. Moreover, the accessibility of equipment in most hospitals is poor, and fluorescence qualitative analysis is still the main method with strong popularity [24] [25] [26]. Therefore, further multi-institutional and large-sample clinical studies are needed in the future to confirm the clinical effect of ICG fluorescence technology. The results of this study will provide a solid foundation for further research in the future.

5. Conclusion

In traditional laparoscopic colorectal cancer surgery, the surgeon's method assess intestinal stumps blood supply is time-consuming and lacks accuracy. ICG real-time indocyanine green fluorescence angiography can guarantee a rapid and reliable anastomosis during laparoscopic radical resection of rectal cancer. This technique reduced postoperative anal ventilation time and postoperative complications to a certain extent and is especially suitable for patients with lower rectal cancer. Further prospective randomized controlled trials from multiple centers with larger sample sizes and longer follow-up periods may confirm that ICG can decrease the rate of postoperative complications and thereby improve outcomes of colorectal cancer surgery.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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